REMARKS

Claims 3-13, 15-36, and 38-61 are currently pending in the application. Claims 3, 15, 38, and 53 are in independent form.

Applicants wish to express their appreciation for the courtesies extended Applicant's representative, Amy E. Rinaldo, during a telephonic/personal interview conducted March 10, 2005.

Claims 3-13, 15-36, and 38-61 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicants regard as the invention.

The Office Action states that the claims as written are ambiguous because there is a discrepancy with regard to B as recited in the claims and what is disclosed in the specification. However, the specification as originally filed included numerous independent claims that recited that B was defined as recited in the presently pending claims. Additionally, the compound, and specifically B, is specifically disclosed throughout the specification, such that B is defined identically to the definition of the presently pending claims. As this compound structure is specifically disclosed throughout the specification, reconsideration of the rejection is respectfully requested.

Claims 3-7, 12, 15-20, 34, 38-43, 46-51, and 53-60 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Albert et al (US Patent No. 5,686,410). Albert does not teach or suggest the claimed compounds, complexes or methods for the reasons indicated below.

Applicants maintain that the Examiner has not established a *prima facie* case of obviousness. To do so, three basic criteria must be met.

> "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) and MPEP Section 2143.

The Office Action states that the Albert et al. patent discloses biologically active peptides selected from growth factors, peptide hormones, interferon, and cytokines that bear at least one chelating group linked to an amino group of the peptide. In addition, the chelating group is capable of complexing with a detectable element for use as a pharmaceutical (radiopharmaceutical for *in vivo* imaging or targeting tissues or therapy). Additionally, the Office Action states that it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to use the gastrin releasing hormone because in claim 1 of the Albert et al. patent, the biologically active peptides may be selected from growth factors, insulin, LHRH, GRP etc. The Office Action concludes that a skilled practitioner in the art would be motivated to select one of the peptides listed by the Albert et al. patent to be conjugated to a chelating group in a detectable label. However, the were numerous compounds listed in the Albert et al. patent and the preferred compounds were all antagonists. In other words, the Albert et al. patent discloses the desirability of an antagonist for use in treating patients. Additionally, as stated previously, GRP is considered to be an autocrine growth factor as established by the previously submitted Walsh et al., 1991, article. GRP has been shown to stimulate the growth of cells in culture and tumors and is therefore considered to be an agonist. Many individuals skilled in the art have been hesitant to use this compound in treating cancer based on the propensity of the GRP to stimulate growth. The growth stimulation occurs because the binding of GRP receptor agonists increases the rate of cell division. A great deal of work has been and is being pursued to develop BBN or GRP analogs that are antagonists, as stated in the present application at page 3, line 14, through page 4, line 1. Antagonists are created by removing the final amino acid and amidating the compound, thereby producing antagonists that can be used *in vivo* to block agonists. Since the Albert et al. patent shows a strong preference for use of an antagonist, a skilled practitioner in the art would not be motivated to select the agonist form of bombesin for use in treating patients.

Further, even if a person of skill in the art were to select an agonist, the Albert et al. patent fails to disclose the combination GRP agonist having a bombesin agonist moiety as claimed by Applicants. The Albert et al. patent discloses the

preparation of a "**biologically active**" peptide selected from growth factors, peptide hormones (such as gastrin releasing peptide or an agonist thereof), interferons and cytokines bearing at least one chelating group linked to an amine group of said peptide, the chelating group being capable of complexing a detectable element such as radionuclide. Column 1, lines 22-30 and column 2, line 11. The term "biologically active" means the retention of the original biological activity of the peptide after attaching the chelating group to it. This is not a trivial matter because peptide hormones such as gastrin releasing peptide have three dimensional structures that allow them to specifically bind to receptors such as gastrin releasing peptide receptors on a cell surface, become internalized inside the cell, and provide a biological response. Once a peptide hormone like the gastrin releasing peptide or an analogue thereof is modified, for example by adding a chelating group to it, there can be no expectation that it would maintain its ability to bind and biologically activate the gastrin releasing peptide receptor and illicit a biological response. The Albert et al. patent did not disclose a single working example of a biologically active gastrin releasing peptide or an analogue thereof attached to a chelating group.

Additionally, the Albert et al. patent also does not provide any reasonable expectation of success to prepare a compound according to the present invention. Such compounds comprise a metal complexed with a chelating group attached to a gastrin releasing peptide (GRP) receptor agonist such that the gastrin releasing peptide receptor agonist includes a bombesin agonist binding moiety. In addition the compound of the present invention must bind a gastrin releasing peptide receptor on a cell surface and be internalized within said cell.

This lack of expectation of success for the preparation of a compound according to the present invention was shared by the Patent Office during the prosecution of the Albert et al. patent. Initially, the Albert et al. patent's applicants submitted a broad claim (original claim 1) to cover a biologically active peptide selected from the group consisting of growth factors, insulin, LHRH, gastrin, gastrin releasing peptide, thyrotropin releasing hormone, thyroid stimulating hormone, prolactin, vasoactive intestinal peptide, angiotensin, interferons, Il-1, Il-4 and Il-6, and analogues or derivatives thereof and bearing at least one chelating group linked to

said peptide. In a May 29, 1996 Office Action (attached herewith as Exhibit A), the Patent Office rejected the broad claims of the Albert et al. patent under §112, first paragraph stating that there is insufficient exemplification and biological data in the application to support biologically active peptides other than epidermal growth factor (EGF). In fact, the only data disclosed by the Albert et al. patent relates to EGF. The Examiner cited the lack of predictability in preparing biologically active peptides except for EGF with a chelating moiety attached thereto. In an October 29, 1996 Amendment (attached herewith as Exhibit B), the Albert et al. patent's applicants amended their claims to limit the biologically active peptides to EFG alone, thereby acceding to the Examiner's rejection.

Accordingly, there can be no reasonable expectation of success based on the teachings of the Albert et al. patent combined with the general knowledge in the art to prepare a compound which comprises a metal complexed with a chelating group attached to a gastrin releasing peptide (GRP) receptor agonist such that the gastrin releasing peptide receptor agonist includes a bombesin agonist binding moiety and is able to bind a gastrin releasing peptide receptor on a cell surface and be internalized into said cell. In fact, the first time a person skilled in the art had this reasonable expectation of success is based on the present disclosure. The present specification discloses for the first time working examples of compounds of the present invention (Figures 30 and 31). Indeed, the present specification shows for the first time that a gastrin releasing peptide analogue (such as bombesin or derivatives thereof) can be modified by adding a chelating group and still be able to bind a gastrin releasing peptide receptor on a cell surface and be internalized into the cell. Since the Albert, et al. patent does not disclose or suggest the invention recited in the presently pending independent claims, the claims are patentable over the Albert et al. patent and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above. The prior art references do not disclose the characterizing

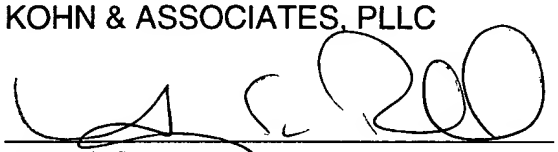
features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES, PLLC



Amy E. Rinaldo
Registration No. 45,791
30500 Northwestern Highway
Suite 410
Farmington Hills, Michigan 48334
(248) 539-5050

Dated: March 17, 2005

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

Express Mail Mailing Label No.: EV 659077403US
Date of Deposit: March 17, 2005

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office To Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Mail Stop: Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

_____
Connie Herty

EXHIBIT A

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/276,280	07/18/94	ALBERT R	1007530PCTCO

PRICKRIL, EXAMINER

18N1/0529

ROBERT S HONOR
SANDOZ CORP
59 ROUTE 10
E HANOVER NJ 07936

ART UNIT	PAPER NUMBER
1813	9

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

DATE MAILED: 05/29/96

■ This application has been examined ■ Responsive to communication filed on 1813 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 MONTHS from the date of this letter.
Failure to respond within the time period will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENTS ARE PART OF THIS ACTION:

1. ■ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ■ Claims 1-28 are pending in the application.
   Of the above claims, 25-27 are withdrawn from consideration.
2. ☐ Claims ___ have been cancelled.
3. ☐ Claims ___ are allowed.
4. ■ Claims 1-24 and 28 are rejected.
5. ☐ Claims ___ are objected to.
6. ☐ Claims ___ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on ___. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on ___ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on ___ has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under 35 USC 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. ___; filed on ___.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

Status of Claims

1. Claims 1-28 are pending in this Office action. Claims 25-27 are withdrawn as being drawn to a nonelected invention.

2. Applicant's election of Group II, claims 1-24 and 28 is acknowledged. The requirement for election of a detectable element is withdrawn in light of applicant's arguments in the response filed 1/22/96.

The elected compound was not found in a search of the prior art. Therefore the search has been expanded to include other compounds embraced by the claim definitions.

Specification

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e.., as failing to provide an enabling disclosure.

The various criteria to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112 were described in *Ex parte Forman*, 230 USPQ 150 (CCPA 1977), and include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the breadth of the claims, the amount of direction

or guidance present, the quantity of experimentation necessary, the relative skill of those in the art, and the presence or absence of working examples. The following is an analysis of these factors in relationship to this application.

Applicants invention is directed to chelators wherein the chelating moiety is conjugated to a peptide chosen from a wide range of common art-recognized proteins or peptides. In the broadest embodiment the chelator, which is capable of being complexed to any "detectable element", is not chemically defined, but in preferred embodiments is based on one of the common art-recognized chelators such as EDTA or DTPA but can be macrocyclic or acyclic. Virtually all aspects of applicant's chelator-peptide conjugates are well known in the art and are either anticipated or rendered obvious by the prior art.

The predictability within the chelator art is low with respect to therapeutic efficacy. This is true in particular for the peptide-chelators of the instant invention due to both the extreme breadth of the number and type of peptides and/or chelators embraced by the claims and to the inherent uncertainty with respect to essential features such as target affinity or in vivo stability can be assessed. While presenting an enormous array of potential embodiments for both the chelating moiety and the associated peptide, applicants present a mere handful of examples which are limited to derivatives of only one chelator moiety (DTPA) and biological data related to only one of the thousands of potential peptides (mEGF). Essentially, applicant's claims are drawn to thousands of peptides and/or chelators for which scant or no enabling support exists, either directly or indirectly, in the specification. For example, a wide variety of macrocyclic chelators are recited at pages 7-9 of the specification which receive no

further support with respect to their biological efficacy. This support is necessary, however, in order to provide the artisan a means of determining which of the thousands of chelating moieties in the description can be coupled to which of the thousands of disclosed peptides in order to assess efficacy. It is unclear how the artisan would go about choosing which combinations of peptide and chelator moiety would be operative absent representative examples of these combinations. Applicants failure to provide any support by way of example for the vast majority of peptides and chelators embraced by the claims would effectively force the artisan to carry out burdensome and undue experimentation, and therefore renders the claims nonenabled.

Claim rejections

4. Claims 1-24 and 28 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

5. Claims 1-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, and 3 are unclear with respect to the meaning of "such amino group". Also, it is unclear what "target receptors" refers to in the ultimate line of these claims or in the last line of claim 19(a). A host of peptides and derivatives are recited which may or may not have receptors. Where are these receptors located?

In claim 4 is the attachment to the amino group covalent, or is any association (ionic?, Vander Waals?) acceptable to meet the claim limitations?

What is a "physiologically peptide" in the first line of claim 9?

The peptides of claims 11 and 12 appear to define peptides having no chelating moiety present (see structures VII, IXa and IXb, for example) What, if any, chelator moiety is present in these claims?

In claim 13 what is "the terminal amino group"? Does this refer to any terminal amino group such as that of lysine, or only to the amino terminal group of the peptide?

Claim 15 is drawn to "a peptide" but appears to claim the ensemble of peptides due to the presence of "and" in the penultimate line. What is intended?

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-5, 8-10, 13, 14, and 16-24 are rejected under 35 U.S.102(b) as being anticipated by Olson [U.S. Patent No. 4,672,028]. Olson discloses peptides and chelating peptides which are identical to those claimed by applicants. For example, some of the peptides of claim 1 are recited at col. 2 lines 63-68, and these are disclosed as metal-chelate conjugates. Furthermore, the radioisotopes of Olson recited at col. 3 lines 50-59 are identical to those of applicants.

8. Claims 1, 3, and 11 are rejected under 35 U.S.C. § 102(a) as being anticipated by Kovacs et al. [*Peptides* **10**, 925-932 (1989), abstract]. Kovacs et al. disclose peptides identical to those claimed by applicants.

9. Claims 1, 2, and 12 are rejected under 35 U.S.C. § 102(a) as being anticipated by Kuranov et al. [*Biorg. Khim.* **15**, 748-762 (1989), abstract]. Kuranov et al. disclose bombesin analogs which are identical to those claimed by applicants.

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

11. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed. 2nd 545 (1966), 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103 are summarized as follows:

1. Determining the scope and contents of the prior art;
2. Ascertaining the differences between the prior art and the claims at issue; and
3. Resolving the level of ordinary skill in the pertinent art.

12. Claims 1-10, 13-24 and 28 are rejected under 35 U.S.C. § 103 as being unpatentable over Fritzberg et al. or EP 103558 (Soini et al.) or EP 243929 (Offord et al.) in view of Bell or Murray et al.

Fritzberg et al. or EP 103558 or EP 243929 disclose protein conjugated chelated metal radionuclides for in vivo use. The only difference between the claimed invention and the aforementioned prior art is that the prior art does not list all of the specific peptides recited by applicants. The peptides of applicant are well known in the art and are not themselves novel in any way. For example, Bell teaches epidermal growth factor (EGF) and Murray teaches PDGF analogs. Furthermore Bell and Murray teach that these peptides can be attached to reporter groups including chelator molecules for various uses. Like the peptides, the chelator molecules disclosed by applicants are conventional and well known in the art. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to attach various chelators to the peptides of Fritzberg et al. or Bell or Murray in order to obtain applicant's invention.

13. No claims are allowed.

General information regarding further correspondence

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1813.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Benet Prickril whose telephone number is (703) 305-5933. The examiner normally can be reached Monday through Thursday between 7:30 AM and 5:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christine Nucker, can be reached at 308-4028. The fax phone number for Art Unit 1813 is (703) 305-7939.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ROBERT D. BUDENS
PRIMARY EXAMINER
GROUP 1800

PTO 892	SERIAL NUMB	Art Unit	Attachment to Paper Number
U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE NOTICE OF REFERENCES CITED	08/276280	1813	9
	APPLICANTS:		

U.S. PATENT DOCUMENTS

*		DOCUMENT NUMBER	DATE	NAME(S)	CLASS	SUBCLASS	FILING DATE

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS	PERTINENT DRW SPEC	

*		OTHER REFERENCES (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)
	A	Kovacs, M. et al., Effects of long-term administration of a superactive agonistic and an antagonistic GNRH analog on the pituitary-gonad, *Peptides* (Elmsford) 10, 925-932 (1989). See entire abstract.
	B	Kuranov, I. et al., Amphibian bombesin and its analogue alytesin, *Biorg. Khim.* 15, 748-762 (1989). See entire abstract.

EXAMINER	DATE	* A COPY OF THIS REFERENCE IS NOT BEING FURNISHED WITH THIS OFFICE ACTION. [SEE MPEP SECTION 707.05(a)].
Benet Prickril	5/28/96	PAGE 1 OF 1

EXHIBIT B

#10 D
Cases
1/10/19

11/04/96

Case No. 100-7530/PCT/CONT/CONT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

RAINER ALBERT, et al. : Group: 1813

Serial No. 08/276,280 : Examiner: B. Prickril

Filed: July 18, 1994 :

For: POLYPEPTIDE DERIVATIVES :

RECEIVED
NOV 1 1996
GROUP 1800

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on October 29, 1996
(Date of Deposit)
Thomas O. McGovern
Name of Person Signing
Thomas O. McGovern
Signature
October 29, 1996
Date of Signature

AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In response to the Office Action of May 29, 1996 on the above indentified application, please amend the application as follows:

IN THE SPECIFICATION

Page 1, last line of the cross reference, after the year "1991", insert the expression -- both of which are -- .

Page 1, last line of the cross reference, after the word "abandoned", insert the expression -- , application Serial No. 07/671,763 being a 371 of PCT/EP90/01169, filed July 12, 1990 -- .

D1

IN THE CLAIMS

Please cancel claims 1 to 3, 9, 11, 12, 15, 16, 19, 22, and 24 to 27.

240 EK 19-0134 01/07/97 08276280
23095 116 350.0008

Claim 4, line 1, after the word "claim", delete the terms "1 or 3", and insert in its place the number -- 29 -- .

Claim 5, line 1, after the word "claim", delete the terms "1 or 4", and insert in its place the number -- 29 -- .

Claims 6 to 8, 13, and 14 and 28, line 1, after the word "claim", delete the number "1", and insert in its place in each instance the number -- 29 -- .

Claim 10, line 1, after the word "or", delete the number "9", and insert in its place the number -- 30 -- .

Claim 13, line 2, after the word "the", delete the word "terminal", and insert in its place the term
-- N-terminal -- .

Claim 17, line 1 and claim 18, lines 1 and 2, after the word "claim", delete the terms "1 or 9", and insert in their place in each instance the terms
-- 29 or 30 --

Claim 17, lines 2 and 3, after the word "form", delete the expression "for use as a pharmaceutical".

Claims 20 and 21, line 1, and claim 23, line 2, after the word "claim", delete the number "19", and insert in its place in each instance the number -- 34 -- .

Please add the following new claims 29 to 36.

29. A peptide in free base or salt form comprising EGF having at least one chelating group capable of complexing a detectable element covalently linked to an amino group of said EGF having no significant binding affinity to target EGF receptors.

30. A peptide in free base or salt form comprising EGF having a chelating group capable of complexing with a detectable element covalently linked either directly or indirectly by means of a divalent bridging group to an amino group of said EGF having no significant binding affinity to target EGF receptors, the chelating group being selected from N'-p-iso-thiocyanatobenzyl-diethylene triamine-N,N,N'',N''-tetraacetic acid;

N'-p-isothiocyanatophenethyl-diethylene triamine-N,N,N'', N''-tetraacetic acid;

N-{2-[bis(carboxymethyl)amino]ethyl}-N'-{2-[bis(carboxymethyl)amino]-2-(p-isothiocyanatobenzyl)-ethyl}-glycine;

DOTA;

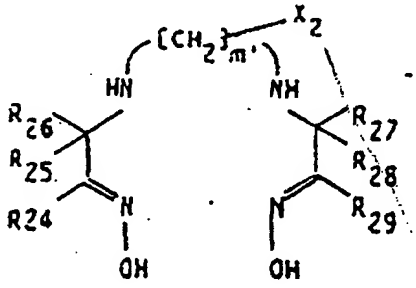
C-functionalised tetraazacyclododecane-tetraacetic acids;

C-functionalised tetraazacyclotetradecane-tetraacetic acids;

C-functionalised triazacyclododecane triacetic acids;

C-functionalised triazacyclononane triacetic acids; and

a compound of formula V



(V)

wherein

each of R_{24}, R_{25}, R_2 R_{26}, R_{27}, R_{28} and R_{29} independently is hydrogen or C_{1-4}alkyl,

m' is 2 or 3, and

X_2 is p-isothiocyanato-benzyl or -phenethyl.

31. The ~~compound~~ peptide according to claim ~~29~~ 37 ~~which~~ which is ~~DTPA~~-mEGF. diethylenetriamine pentaaceti

32. The ~~compound~~ peptide according to claim ~~29~~ 37 which is p-isothiocyanatobenzyl-~~DTPA~~-mEGF. diethylenetriamine pentaacetic acid

33. The ~~compound~~ peptide according to claim ~~29~~ 37 which is p-isothiocyanatobenzyl-~~DOTA~~-mEGF. 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid

34 . A chelate in free base or pharmaceutically acceptable acid addition salt form comprising EGF having

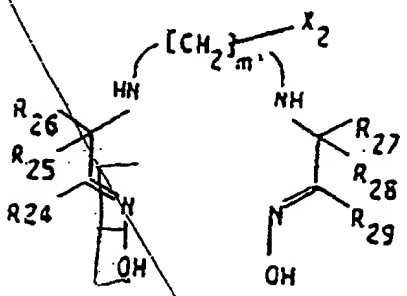
a) at least one chelating group capable of complexing with a detectable element covalently linked to an amino group of EGF having no significant binding affinity to target EGF receptors; or

b) a chelating group capable of complexing with a detectable element covalently linked either directly or indirectly by means of a divalent bridging group to an amino group of EGF having no significant binding affinity to target EGF receptors, the chelating group being derived from

N'-p-isothiocyanatobenzyl-diethylene triamine-N,N,N'',N''-tetraacetic acid;

N'-p-isothiocyanatophenethyl-diethylene triamine-N,N,N'', N''-tetraacetic acid;

N-{2-[bis(carboxymethyl)amino]ethyl}-N'-{2-[bis(carboxy-methyl)amino]-2-(p-isothiocyanatobenzyl)-ethyl}-glycine;
DOTA;
C-functionalised tetraazacyclododecane-tetraacetic acids;
C-functionalised tetraazacyclotetradecane-tetraacetic acids;
C-functionalised triazacyclododecane triacetic acids;
C-functionalised triazacyclononane triacetic acids; and
a compound of formula V



(V)

wherein
each of R_{24}, R_{25}, R_{26}, R_{27}, R_{28} and R_{29} independently is hydrogen or C_{1-4}alkyl,
m' is 2 or 3, and
X_2 is p-isothiocyanato-benzyl or -phenethyl,

complexed with a detectable element.

35. The compound according to claim 34 whion is ^{111}In labeled DTPA-ß-Ala-mEGF.

36. The compound according to claim 34 whion is ^{90}Y labeled DTPA-ß-Ala-mEGF.

REMARKS

Claims 1 to 28 have been presented for examination and claims 4 to 8, 10, 13, 14, 17, 18, 20, 21, 23, and 28 to 36 are now in the application. No additional fee is required.

The Examiner indicates that the election of Group I, claims 1 to 24 and 28 is acknowledged and that the requirement for the election of a detectable element is withdrawn.

The specification is objected to under the first paragraph of 35 USC 112 as failing to provide an enabling disclosure. The Examiner indicates that predictability in the chelator art is low with respect to therapeutic efficacy and that this is particularly true for the peptide-chelators of the instant invention, in view of the large number and types of peptides and chelators embraced by the claims combined with the inherent uncertainties, such as target affinity and in vivo stability. The Examiner further indicates that for this enormous array of potential embodiments, Applicants provide only a small number of examples, which are limited to one chelator moiety (DTPA) and biological data for one peptide, epidermal growth factor (mEGF). The Examiner argues that this would not enable one skilled in the art to determine which peptides and chelator moieties would be operative. The Examiner concludes that absent representative examples, one would have to carry out burdensome and undue experimentation; and therefore, the claims are not enabled. Claims 1 to 24 and 28 are also

rejected under the first paragraph of 35 USC 112 for the same reasons. With regard to the claims now in the application, Applicants respectfully disagree and traverse the rejection.

The Examiner's argument basically is that there is insufficient exemplification and biological data in the instant application to support the scope of the invention claimed. Applicants have amended the claims to limit the ligands and chelates of the invention to EGF, which is believed to be fully supported by the present specification. The only question in this rejection is whether there is sufficient support for the scope of the chelating moieties comtemplated in the invention. Applicants submit that there is. Contrary to the Examiner's argument, exemplification has not only been provided for the polyaminopolycarboxylic ligands by DTPA; but also for the macrocyclic ligands by DOTA in Example 15. It will be noted that there is nothing in the statute or in the case law which requires any exemplification or any biological data in an application in order to meet the requirements of the first paragraph of 35 USC 112. The arguments advanced by the Examiner for this rejection have all been addressed in the the Patent and Trademark Office's Guidelines for Disclosure of Utility in Patent Applications for Drugs" (849 O.G. 567). It will also be noted that Applicants' exemplification and utility statement are in complete conformity with those guidelines. The pertinent portion of the guidelines state that:

"With respect to the adequacy of disclosure that a claimed genus possesses an asserted utility representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if it would be deemed likely by one skilled in the art, in view of contemporary knowledge in the art, that the claimed genus would possess the asserted utility. Proof of utility will be required for other members of the claimed genus only in those cases where adequate reasons can be advanced by the examiner for believing that the genus as a whole does not possess the asserted utility" (Emphasis added)

In the present application, Applicants have provided 6 representative working examples of both ligands and chelates; and on pages 25 and 29, Applicants state that the ligands of the invention as a whole are useful in preparing the chelates of the invention, and the chelates of the invention as a whole possess imaging and therapeutic activity in visualizing and treating receptor-positive tumors and metastases. Applicants are skilled in the art and are not aware of any contemporary reasons why the ligands and chelates would not possess the asserted utilities. The only reasons advanced by the Examiner for believing that the claimed chelate genus does not possess the disclosed utilities is that the application does not provide sufficient examples of chelating moieties and biological data to show that the EGF chelates would be effective in imaging and treating EGF receptor-positive tumors and metastases. This reasoning is incorrect. As indicated above, applicants have provided examples of both polyaminopolycarboxylic and macrocyclic

ligands and chelates; and on pages 44 and 45, EGF binding data is disclose for the ligand and chelate of Examples 3 and 4. The Board of Patent Appeals and Interferences stated in its decision in Ex parte Sudilovsky (21 USPQ 2nd 1702) that the factors adopted by the Board in determining if an application meets the requirements of 35 USC 112 are those set out by the then CCPA in In Re Colianni (195 USPQ 150). These factors, as the Examiner notes, include: 1) the nature of the invention; 2) the state of the prior art; 3) predictability; 4) the amount of direction or guidance present; and 5) the presence of working examples. In the present application, in accord with the reasoning in Sudilovsky: 1) the nature of the invention is such that there is a reasonable likelihood that it will be effective in imaging and treating the conditions claimed by the Applicants; 2) the state of the art including that cited by the Examiner clearly indicates that radiolabeled chelates are recognized as being useful for imaging and treating receptor-positive tissue; 3) the predictability in this art is certainly demonstrated by the fact that the chelating moieties have been used in similar chelates which exhibit analagous imaging and treatment activity; 4) the guidance provided includes highly detailed testing and data relating solely to the utility for the claimed compounds; and 5) the working examples and binding data for the EGF derivatives of Examples 3 and 4 on pages 44 and 45, would certainly lead one skilled in the art to accept Applicants' utility allegations as obviously valid and correct. The information and data provided by Applicants have long been considered sufficient to enable anyone skilled in the art to

make and use the invention claimed without undue experimentation. The Courts, as restated in Sudilovsky, have made it clear that a rejection for lack of enablement must be backed up with acceptable reasons or evidence. Otherwise, Applicants do not have to go to the trouble and expense of providing proof that the teaching of a specification are enabling. (See In re Marzocchi, 169 USPQ 367; or In re Armbruster, 185 USPQ 152). In the present case, the Examiner has clearly not provided the acceptable reasons or evidence required by the courts for alleging that the instant disclosure would not enable one skilled in the art to make and use the invention claimed. Applicants submit that the present application clearly meets the enablement requirements of 35 USC 112 as set out in Sudilovsky; and therefore, it is respectfully requested that the Examiner reconsider the instant rejections under 35 USC 112 and withdraw them.

Claims 1 to 24 are rejected under the second paragraph of 35 USC 112 for the reasons indicated below. Applicants' comments are set out after each of the reasons.

1. The Examiner indicates that claims 1 and 3 are indefinite with respect to the terminology "such amino group", and it is also unclear what the term "target receptors" refers to in these claims and in claim 19. Applicants have deleted claims 1, 3 and 19 from the present application and have replaced them with new claims 29 and 34, in which the amino group and target receptors are more accurately identified.

2. The Examiner asks whether the attachment of the chelator moiety to the amino group in claim 4 is covalent or if any bonding would be acceptable in the invention contemplated. The Examiner also asks what the term "physiologically peptide" in claim 9 means. In new generic claim 29 now in the application, Applicants indicate that the bond between the amino group and the chelator moiety is a covalent bond. Claim 9 has been replaced by new claim 30 in which more accurate peptide terminology is used.

3. The Examiner indicates that claims 11 and 12 appear to cover peptides having no chelator moiety and asks if a chelator is contemplated in the claims. Applicants have deleted claims 11 and 12 from the present application and no further comment regarding these claims is believed necessary.

4. The Examiner asks whether the "terminal amino group" in claim 13 represents an amine group at the end of the peptide or an omega amino group such as in lysine. Applicants have amended claim 13 to indicate that the chelator moiety in the claim is attached to the N-terminal amino acid of the peptide.

5. The Examiner indicates that claim 15 is drawn to a group of peptide but appears to cover an ensemble of compounds due to the presence of the word "and" in the next to last line. Applicants have cancelled claim 15 from the application and no further comment regarding the claim is considered necessary.

In view of the above amendments, Applicants believe that the claims now in the application meet all of the requirements of the second paragraph of 35 USC 112. Accordingly, it is respectfully requested that the Examiner reconsider this rejection of the claims and withdraw it.

Claims 1 to 5, 8 to 10, 13, 14 and 16 to 24 are rejected under 35 USC 102(b) over the Olson United States Patent No. 4,672,028. The Examiner indicates that Olson discloses peptides and chelating agents which are identical to those claimed by Applicants. As indicated above, the claims now in the application are limited to ligands and chelates in which the peptide moiety is EGF. The Olson patent does not disclose or anticipate this peptide; and accordingly, the instant rejection under 35 USC 102(b) is no longer believed to be applicable.

Claims 1, 3 and 11 are rejected under 35 USC 102(a) over the Kovacs, et al. "Peptide" abstract; and claims 1, 2 and 12 are rejected under 35 USC 102(a) over the Kuranov, et al. "Biorg-Khim" abstract. The Examiner indicates that the references disclose peptides identical to those claimed by Applicants. Kovacs and Kuranov do not appear to disclose any chelated compounds in the abstracts and clearly do not disclose the EGF ligands and chelates presently claimed. This rejection is not applicable to the claims now in the application; and accordingly, is respectfully requested that the Examiner reconsider the rejection and withdraw it.

Claims 1 to 10, 13 to 24 and 28 are rejected under 35 USC 103 over the Fritzberg, et al. U.S. Patent No. 5,037,630 or the Soini, et al. European Patent Application 0 103 558 or the Offord, et al.'s European Patent Application 0 243 929 in view of the Bell U.S. Patent No. 4,783,412 or the Murray, et al. U.S. Patent No. 4,801,542 (all of record). The Examiner indicates that Fritzberg, Soini and Offord disclose radiolabelled chelated proteins for diagnostic and therapeutic use. The Examiner also indicates that the only difference between the claimed invention and the prior art is that Fritzberg, Soini and Offord do not disclose the specific peptides claimed by Applicants. However, the Examiner notes that the claimed peptides including EGF are well known in the art and are not novel per se, as shown by the Bell patent which teaches EGF and the Murray patent which teaches platelet derived growth factor (PDGF). The Examiner further notes that the chelator moieties, like the peptides, are also conventional and well known in the art. The Examiner concludes that it would have been obvious to one skilled in the art to attach the various chelator moieties to the peptides of Bell or Murray to obtain the instant invention. Applicants respectfully disagree and traverse the rejection.

As the Examiner indicates, none of the primary references disclose the EGF of the presently claimed invention. Fritzberg is primarily directed to immunoglobulin and immunoglobulin fragments which are useful in the diagnosis and treatment of melanoma cells. Soini is primarily concerned with lanthanide chelates of insulin and to a method for the quantitative determination of a bio-specific affinity reaction in which no separation of the free

and labelled compound is required. The Offord patent application is also primarily concerned with immunoglobulin and insulin chelates in which the chelator is bonded to the C-terminus of the immunoglobulin or insulin. Nothing in these references would suggest or lead one to the EGF ligand of the present invention or its use. The secondary Bell references discloses a DNA molecule containing a nucleotide sequence for encoding human EGF. However, contrary to the Examiner's comment, nothing in Bell suggests forming a radiolabelled chelate of EGF. The only compound labelled with a marker in Bell is the ^{32}P end-labelled oligonucleotide probe in column 5. Clearly, the subject matter of the primary references is totally unrelated to the subject matter of the relevant secondary reference. The Examiner states that predictability in the chelator art is low with respect to therapeutic efficacy, especially with peptide-chelators and the inherent uncertainty in their target affinity and stability. There is no way that one could predict with any degree of certainty what effect a radiolabelled chelating moiety would have on the activity of EGF without trying it, and this is not sufficient for obviousness. The Examiner has selected unrelated patents directed to structurally and functionally dissimilar compounds and has combined them in such a way as to obtain the ligands and chelates of the present application. This has been done without any way of knowing that a combination of the references would be desirable and would result in an active product. In the instant rejection, there is no logical reason apparent in the references cited which would suggest the desirability or justify the combination of the primary and secondary

references in the manner proposed. The Examiner has synthesized Applicants' compound from the broad disclosures of multiple references guided not by the teachings of the art but by the teachings of the present application. The instantly claimed ligands and chelates are clearly patentable over the prior art; and therefore it is respectfully requested that the Examiner reconsider the present rejection under 35 USC 103 and withdraw it.

In addition to new claims 29, 30, and 34, Applicants have also added new claims 31 to 33 and 35 to 39 to cover preferred embodiments of the invention. The basis for the new claims is as follows:

Claim	Basis
29	Original claim 1, page 6, lines 10 to 12; and page 21, line 12;
30	Original claim 9;
31 to 33	Examples 13 to 15;
34	Original claim 19, and page 29, lines 20 and 21; and
35 and 36	Examples 4 and 5.

The new claims are fully supported by the present application, and it is respecfully requested that they be entered.

Applicants have also amended the cross reference on page 1 of the application to insert the current status of parent application Serial No. 08/017,723 and to indicate that grandparent application Serial No. 07/671,763 is a 371 of PCT/EP90/01169, filed July 12, 1990.

The Claim of Priority, and the receipt of the priority documents set out on pages 4 and 5 of the Rule 60 filing papers have not been acknowledged by the Examiner.

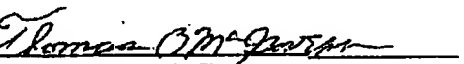
The Information Disclosure Statement submitted with the Amendment of September 21, 1995 has also not been acknowledged by the Examiner; and a copy of form PTO-892 listing the art cited by the Examiner was not received by Applicants with the Office Action of May 29, 1996.

It is respectfully requested that the period for filing a response to the Office Action of May 29, 1996 on the instant application, Serial No. 08/017,723, originally set to expire August 29, 1996, be extended for 2 months until October 29, 1996.

Please charge the extension fee of $390 required by 37 CFR 1.17(b) to Deposit Account No. 19-0134 in the name of Sandoz Corporation.

In view of the above amendments and comment, it is believed that the claims now in the application are patentable over the prior art and in condition for allowance. Accordingly, it is respectfully requested that the Examiner withdraw the present rejection of the claims and pass the application to issue.

Respectfully submitted,

By 
Thomas O. McGovern
Registration No. 25,741
(201) 503-8480

TOM:lmc

SANDOZ CORPORATION
59 Route 10
E. Hanover, N.J. 07936

October 29, 1996

Enclosures: Page 16 of Amendment in triplicate;
Two Month Extension of Time;
COM Stamp; Postcard